B-Type Natriuretic Peptide Predicts Adverse Cardiovascular Events in Pediatric Outpatients With Chronic Left Ventricular Systolic Dysfunction

Jack F. Price, MD; Anne K. Thomas, RN, MSN; Michelle Grenier, MD; Benjamin W. Eidem, MD; E. O’Brian Smith, PhD; Susan W. Denfield, MD; Jeffrey A. Towbin, MD; William J. Dreyer, MD

Background—Plasma B-type natriuretic peptide (BNP) levels are elevated in adults with heart failure and correlate with functional classification and prognosis. The range and predictive power of BNP concentrations in children with chronic heart failure, however, are not known.

Methods and Results—Whole blood BNP concentrations were measured in 53 consecutive patients with chronic left ventricular (LV) systolic dysfunction (biventricular hearts, ejection fraction <50%, >3 months since diagnosis). Children who had been hospitalized within 3 months before potential enrollment and those <2 months or >21 years of age were excluded. BNP concentrations were measured with the Triage assay (Biosite Diagnostics, Inc, San Diego, Calif). Echocardiographers and clinicians were blinded to BNP levels. An adverse cardiovascular event was defined as cardiac death, cardiac-related hospitalization, or listing for cardiac transplantation. The median age of patients with LV dysfunction was 9.3 years (interquartile range [IQR], 2.7 to 15.1 years). BNP levels were elevated in children with LV dysfunction compared with healthy controls (median, 78 pg/mL [IQR, 22 to 551 pg/mL] versus median, 7 pg/mL [IQR, 5 to 11 pg/mL]; P<0.0001). Whole blood BNP concentrations were increased in patients who had a 90-day adverse cardiovascular event compared with those who did not (median, 735 pg/mL [IQR, 685 to 1510 pg/mL] versus median, 37 pg/mL [IQR, 14 to 92 pg/mL]; P<0.001). Patients with a BNP concentration ≥300 pg/mL were at increased risk of death, hospitalization, or listing for cardiac transplantation (adjusted hazard ratio, 63.6; P<0.0001).

Conclusions—BNP concentrations are elevated in children with chronic LV systolic dysfunction and predict the 90-day composite end point of death, hospitalization, or listing for cardiac transplantation. (Circulation. 2006;114:1063-1069.)

Key Words: cardiomyopathy • heart failure • natriuretic peptides • pediatrics

The cardiac hormone B-type natriuretic peptide (BNP) is now widely recognized as a reliable marker of ventricular dysfunction and heart failure in adults. This 32–amino acid peptide is secreted by the ventricular myocardium during situations of increased wall stress caused by excessive volume or pressure loading of the heart.1 Plasma BNP concentrations are elevated in adults with congestive heart failure and can distinguish cardiac from noncardiac causes of dyspnea, correlate with the severity of heart failure symptoms, and predict mortality and hospital readmission.2–9 Because of this relationship, plasma BNP concentrations have become a useful tool in both the acute care and outpatient settings to facilitate with the diagnosis, triage, and risk stratification of adult patients with congestive heart failure.10–13

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Despite the prolific reporting of BNP data in adults with heart failure, very little is known about this hormone in children and even less in children with heart failure. A few small studies have reported normative data for BNP in the pediatric population, but our understanding of the clinical utility of BNP in children with heart failure remains insufficient.14,15 In fact, no studies have evaluated the role of BNP in pediatric patients with chronic heart failure. Therefore, we sought (1) to determine the range of whole blood BNP concentrations in children with chronic left ventricular (LV) systolic dysfunction and (2) to test the hypothesis that BNP concentrations can predict adverse cardiovascular events.

Methods

Study Design

This study was designed as a prospective cohort investigation in which BNP concentrations were measured in consecutive outpatients with chronic LV systolic dysfunction. The Baylor College of Medicine Institutional Review Board approved the study protocol, and procedures were followed in accordance with institutional guidelines, including obtaining written parental consent and, when appropriate, patient assent.
Patient Selection
Subjects were recruited from the outpatient cardiology and heart failure clinic at the Department of Pediatrics, The Lillie Frank Abercrombie Section of Pediatric Cardiology, Baylor College of Medicine, Texas Children’s Hospital, Houston. The study protocol included symptomatic and asymptomatic patients who had been treated with standard medical therapy for LV systolic dysfunction (ejection fraction [EF] <50%) for at least 3 months. Patients <2 months or >21 years of age were excluded from the study. In addition, patients whose systolic dysfunction was attributable to left-sided obstructive lesions, anyone hospitalized for exacerbation of heart failure symptoms in the preceding 3 months, and patients with a history of structural heart disease or renal failure were also excluded. Healthy children who underwent screening echocardiography in the cardiology outpatient clinic because of an abnormal ECG or heart murmur were enrolled as control subjects. All controls had normal echocardiograms and no evidence of active disease processes.

Echocardiography and Physician Assessment
An echocardiogram was performed on each study patient at the time of enrollment, and LVEF was estimated with the use of the Simpson biplane method. Other echocardiographic measurements obtained included LV end-diastolic dimension (LVEDD), transmitral early diastolic velocity/tissue Doppler early diastolic mitral annular velocity (E/Ea), and myocardial performance index (MPI).16 The LVEDD was expressed as a deviation from the mean (Z score). Pulsed Doppler was used to determine transmitral blood flow velocity in the apical 4-chamber view. Tissue Doppler velocities were measured at the lateral mitral annulus. A clinical history was taken before BNP measurement was performed. The association of categorical variables with high or low BNP concentrations was predictive of the composite end point over the 90-day time process.

Primary End Point
The primary end point was the occurrence of an adverse cardiovascular event at 90 days. An adverse cardiovascular event was defined as cardiac death (pump failure or sudden death), hospitalization for cardiac reasons (new onset or worsening of heart failure symptoms), or new listing for cardiac transplantation. When risk of adverse events was determined, patients in whom >1 adverse event occurred were treated as though they had only 1 event.

Measurement of BNP
Plasma BNP levels in study and control subjects were measured in the outpatient clinic with the use of the point-of-care Triage Meter Plus assay (Biosite Diagnostics, Inc, San Diego, Calif). Approximately 250 μL of whole blood was sampled from each subject. The assay can reliably detect BNP concentrations ranging from 5 to 5000 pg/mL and has a coefficient of variation of 9.9% to 12.2%. Both echocardiography staff and clinic physicians were blinded to the BNP values.

Statistical Analysis
Continuous variables are expressed as mean (±SD) or median (interquartile range [IQR]) depending on the distribution of the variable. Groups were compared with the use of either a t test or the Mann-Whitney U test, depending on normality and variance assumptions. The association of categorical variables with high or low BNP concentration was determined by χ² analysis. Pearson correlation was used to determine correlation between BNP and echocardiographic variables. Receiver operating characteristic (ROC) curves were generated to determine the accuracy and optimal threshold of BNP and echocardiographic measurements for predicting future adverse cardiovascular events. We compared the areas under the ROC curves using the Hanley-McNeil method.15 Cox proportional hazards regression was used to determine whether BNP concentrations were predictive of the composite end point over the 90-day time from enrollment. The time to the earliest adverse event was used for creation of a Kaplan-Meier curve. A probability value <0.05 was considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
Patient Characteristics
Sixty-three consecutive patients met eligibility criteria, and 53 were enrolled (see Table 1 for patient characteristics). Ten
eligible patients were not enrolled because of refusal of a parent to give consent, failure of the investigator to seek enrollment before the patient left the clinic, or unsuccessful phlebotomy. The median age of enrollees was 9.3 years (IQR, 2.7 to 15.1 years), and the median time from diagnosis of LV dysfunction was 22 months (IQR, 5 to 42 months). Fifty-five percent of study subjects had been hospitalized previously for an exacerbation of heart failure symptoms. Eighteen healthy control subjects were also enrolled (median age, 7.9 years; IQR, 3.8 to 13.1 years). The median BNP concentration was 78 pg/mL (IQR, 22 to 551 pg/mL) in study subjects and 7 pg/mL (IQR, 5 to 11 pg/mL) in controls. Whole blood BNP concentrations were significantly greater in study subjects than in control subjects (median, 78 pg/mL [IQR, 22 to 551 pg/mL] versus median, 7 pg/mL [IQR, 5 to 11 pg/mL]; P<0.0001).

**Echocardiography Data**
Median values and ranges of LVEF, LVEDD Z score, LV MPI, and mitral E/Ea are listed in Table 1. Whole blood BNP concentrations correlated with LVEF (r = -0.53, P < 0.001) and LV MPI (r = 0.45, P < 0.002) but did not correlate with LVEDD Z score (r = 0.2, P > 0.2) or mitral E/Ea (r = 0.14, P < 0.15). Those patients with at least moderate mitral regurgitation had higher BNP concentrations than patients with less than moderate mitral regurgitation (median, 701 pg/mL [IQR, 192 to 1272 pg/mL] versus median, 48 pg/mL [IQR, 16 to 195 pg/mL]; P < 0.003).

**Signs and Symptoms**
Twenty-one study subjects had at least 1 sign or symptom of heart failure at the time of enrollment. Clinical findings included fatigue or decreased activity level (n = 15); dyspnea, orthopnea, or increased work of breathing (n = 10); gallop rhythm (n = 9); hepatomegaly (n = 8); peripheral edema (n = 4); syncope or near syncope (n = 3); rales (n = 2); and diaphoresis (n = 1).

**Adverse Cardiovascular Outcome**
Follow-up data were available for all 53 study subjects. At 90 days after BNP testing, 19 adverse cardiovascular events had occurred in 15 patients. Three patients died from pump failure, 4 patients were listed for cardiac transplantation, and there were 12 hospitalizations for new onset or worsening of heart failure symptoms. Whole blood BNP concentration was significantly greater among patients in whom an adverse event occurred than in patients in whom no adverse event occurred (median, 735 pg/mL [IQR, 685 to 1510 pg/mL] versus median, 37 pg/mL [IQR, 14 to 92 pg/mL]; P < 0.001) (Figure 1).

**LV Dysfunction With “Normal” BNP Concentrations**
Seventeen patients with LV dysfunction had “normal” BNP concentrations (ie, <30 pg/mL). Compared with subjects with BNP concentrations ≥30 pg/mL, they had a higher LVEF (40±8% versus 33±11%; P < 0.02), lower LVEDD Z score (2.0±1.5 versus 3.5±2.1; P < 0.02), lower LV MPI (0.50±0.13 versus 0.62±0.16; P < 0.03), and lower mitral E/Ea (6.0±2.3 versus 10.0±5.9; P < 0.002). They were also less likely to have signs or symptoms of heart failure (3/17 versus 18/36; P < 0.04), and none of them suffered an adverse cardiovascular event.

**Prognostic Accuracy**
To determine the accuracy of a whole blood BNP concentration for predicting an adverse cardiovascular event, a ROC curve was generated. The area under the curve was 0.98 (95% confidence interval [CI], 0.96 to 1.0; P < 0.0001), indicating a high degree of prognostic accuracy. A cutoff BNP concentration of 282 pg/mL was found to be the optimal value for discriminating patients at risk for future adverse cardiovascular events. ROC curves were also plotted for LVEF, LVEDD Z score, LV MPI, and mitral E/Ea. The area under the ROC curve for BNP was significantly greater than the area under the ROC curves for LVEF (0.75; P < 0.001), LVEDD Z score (0.65; P < 0.001), LV MPI (0.8, P < 0.03), and mitral E/Ea (0.62, P < 0.001). Optimal cutoff values for each echocardiographic feature included an LVEF of 35%, an LVEDD Z score of 2.6, an LV MPI of 0.64, and a mitral E/Ea of 6.9. The sensitivity, specificity, and predictive values for each cutoff value, including a BNP concentration of 300 pg/mL and the presence or absence of heart failure signs or symptoms, are listed in Table 2. A BNP concentration cutoff of 300 pg/mL had the highest sensitivity, specificity, and predictive values (sensitivity, 0.93; 95% CI, 0.66 to 0.99; specificity, 0.95; 95% CI, 0.81 to 0.99; positive predictive value, 0.88; 95% CI, 0.6 to 0.98; negative predictive value, 0.97; 95% CI, 0.84 to 0.99). Both the LV MPI and the presence of heart failure signs or symptoms had weak positive predictive values but strong negative predictive values, whereas LVEF, LVEDD Z score, and mitral E/Ea all had relatively weak predictive values.
BNP <300 pg/mL Versus BNP ≥300 pg/mL

After adjustment for age and gender, subjects with a BNP concentration ≥300 pg/mL were found to be at increased risk of having an adverse cardiovascular event within 90 days of testing (adjusted hazard ratio = 3.9; P < 0.003). They also had a lower LVEF (28 ± 11% versus 38 ± 9%; P < 0.001) and greater LV MPI (0.7 ± 0.1 versus 0.5 ± 0.1; P < 0.001) than subjects with a BNP concentration <300 pg/mL. Although there was a trend toward an increased LVEDD Z score among subjects with a BNP concentration ≥300 pg/mL, the difference in means was not statistically significant (3.9 ± 2.8 versus 2.7 ± 1.6; P = 0.2). Similarly, there was no difference in E/Ea between the groups (10.9 ± 5.6 versus 8.1 ± 5.4; P < 0.2). Patients with BNP levels ≥300 pg/mL were also more likely to have signs or symptoms of heart failure (13/16 versus 9/37; P < 0.001). Nine of 14 patients (64%) with at least moderate mitral regurgitation had a BNP concentration ≥300 pg/mL. Eight (89%) of those patients subsequently suffered an adverse cardiovascular event. Only 1 patient of 37 with a BNP concentration <300 pg/mL met the primary end point, whereas 14 of 16 patients in the group with a BNP ≥300 pg/mL remained at risk at 90 days. A Kaplan-Meier curve demonstrates the cumulative freedom from adverse cardiovascular events over time for patients with a BNP <300 pg/mL and patients with a BNP ≥300 pg/mL (Figure 2). This difference was highly significant (P < 0.001).

Discussion

These data demonstrate that whole blood BNP concentrations are increased in children with chronic LV systolic dysfunction compared with healthy children. Additionally, BNP concentrations were found to range widely in this population. In fact, some children with LV dysfunction have BNP levels within a range that previously has been described as normal (i.e., <30 pg/mL). Moreover, BNP concentrations predicted the 90-day composite end point of death, hospitalization, or listing for cardiac transplantation. A BNP concentration of ≥300 pg/mL, in particular, appeared to be a strong discriminator of patient morbidity and mortality.

Previous reports have suggested that BNP concentrations are elevated in children with ventricular dysfunction. Studies in children, however, have been limited by the relatively small number of eligible subjects or restriction to a cohort with a particular comorbidity (e.g., Duchenne muscular dystrophy) or confounded by the inclusion of patients with various types of structural heart disease and cardiac physiologies. With respect to anatomy, physiology, and medical therapy, the cohort in the present study was relatively homogeneous in that all subjects had biventricular hearts with depressed LV systolic dysfunction, and the vast majority were treated with an angiotensin-converting enzyme inhibitor and/or a β-blocker.

Elevated BNP and LV Dysfunction

Our findings of elevated BNP concentrations in children with chronic LV dysfunction are consistent with neurohormonal data reported in adults. Tsutamoto and colleagues found that BNP concentrations were wide ranging in adults with chronic heart failure and that most adult patients (NYHA class II to III) had levels <250 pg/mL. Similarly, our observation that a significant portion of the present cohort had a BNP concentration considered normal has also been described in adults with LV systolic dysfunction.

<table>
<thead>
<tr>
<th>TABLE 2. Sensitivity, Specificity, and Predictive Values of Clinical Evaluations</th>
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<tr>
<td>BNP ≥300 pg/mL</td>
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<td>Heart failure signs or symptoms</td>
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<td>LV MPI &gt; 0.64</td>
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<td>LVEF &lt; 35%</td>
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<td>LVEDD Z score &gt; 2.6</td>
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<td>Mitral E/Ea &gt; 6.9</td>
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<td>Values in parentheses are 95% CI. PPV indicates positive predictive value; NPV, negative predictive value.</td>
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Figure 2. Kaplan-Meier plot of cumulative freedom from adverse cardiovascular events for patients with BNP concentrations <300 or ≥300 pg/mL, demonstrating a greater incidence of adverse events for the latter group (P < 0.001). Among patients with a BNP <300 pg/mL, 36 of 37 remained at risk of the primary end point at 90 days compared with 2 of 16 in the group with a BNP concentration ≥300 pg/mL.
colleagues reported that up to 21% of adult patients with chronic symptomatic heart failure had BNP concentrations below those considered diagnostic of heart failure (<100 pg/mL). Approximately one third of our cohort had a normal BNP level (<30 pg/mL) and, interestingly, 3 patients with normal BNP levels and LV dysfunction also had signs or symptoms of heart failure. Despite being symptomatic, none of those patients suffered an adverse cardiovascular event within 90 days of assessment.

In the present study, BNP was found to be a strong predictor of cardiac mortality and morbidity in children with chronic LV systolic dysfunction. The 90-day adverse cardiovascular event rate among patients with BNP concentrations ≥300 pg/mL was 88%. These findings are similar to reports in adults with heart failure in which baseline BNP concentrations and changes in BNP over time predicted both mortality and morbidity. Among patients with stable but symptomatic heart failure in the Valsartan Heart Failure Trial, the relative risk of mortality or first morbid event was 2.1 for patients with a baseline BNP concentration above the median (97 pg/mL).

Clinical Correlation

Echocardiographic and symptomatic heart failure data could predict adverse cardiovascular events in this cohort to some degree but not with the accuracy of BNP. The echocardiographic measurement with the most satisfactory predictive power for adverse cardiovascular events was the LV MPI (negative predictive value, 97%), a ratio of ventricular relaxation and contraction times that is influenced by both systolic and diastolic properties. The fact that BNP is released in patients with isolated diastolic dysfunction may explain why the LV MPI correlated better with BNP concentrations than some of the other echocardiographic measures. The mitral E/Ea is also affected by diastolic filling; however, we found no correlation between it and BNP. The sensitivity, specificity, and predictive powers of the mitral E/Ea were relatively weak for the primary end point. Calculating the ratio of transmural diastolic velocity to tissue Doppler annular velocity is a method of estimating LV filling pressures and has been shown to predict outcomes in adults hospitalized with congestive heart failure. In adults, it is also known to have a diagnostic accuracy for congestive heart failure similar to BNP. Although the LVEF correlated indirectly with BNP, the more evenly distributed values about the optimal cutoff point of 35% made it a less reliable predictor of adverse events. Similarly, the predictive power of LVEDD Z score was marginal and did not correlate with BNP concentration.

The absence of signs or symptoms of heart failure by medical history and physical examination could help to rule out a future adverse event. The presence of symptoms, however, could not predict a positive event. The poor correlation with BNP and the comparably weak predictive powers of echocardiographic and clinical data suggest that BNP concentration alone may more reliably predict short-term adverse cardiovascular events in children than other standard outpatient evaluation tools.

The accuracy with which BNP predicted clinical deterioration in this cohort speaks more to the ability of this test to reflect the patients’ degree of clinical compensation than its prediction of impaired ventricular contractility. Of 16 patients with an EF ≤30% in this study, 4 (25%) had normal BNP concentrations. More accurately, this regulatory hormone is a surrogate marker of circulatory compensation, and there is growing evidence in adults to support this concept. Kazanegra and colleagues demonstrated that falling BNP concentrations parallel the drop in pulmonary capillary wedge pressure in adult patients treated for decompensated heart failure. Maisel and colleagues found that BNP levels in adults with heart failure differed significantly as a function of the severity of heart failure symptoms and correlated with NYHA functional classification. Likewise, Lee and colleagues reported the superiority of BNP compared with LVEF for assessing functional classification during the treatment of chronic heart failure. Furthermore, plasma BNP concentrations have been shown to be associated with exercise capacity in adult patients with chronic heart failure, correlating with the impairment of VO2 at peak exercise and anaerobic threshold.

As a marker of circulatory compensation, BNP may have valuable adjunctive clinical utility in infants and small children, among whom signs of heart failure commonly are not recognized until overt decompensation occurs and in whom symptoms may not be adequately articulated. We speculate that a measured BNP concentration may be additive to the current clinical assessment of children with chronic LV dysfunction and may help to distinguish those patients at risk of future adverse cardiovascular events. Another subgroup of patients who might benefit from BNP testing is the cohort with at least moderate mitral regurgitation. Systolic ventricular function frequently belies the severity of disease in these patients, and BNP may aid in identifying those at increased risk. All but 1 patient with at least moderate mitral regurgitation who subsequently suffered an adverse cardiovascular event had a baseline BNP concentration >300 pg/mL. Further studies will be necessary to determine a role for BNP in risk stratification of pediatric patients and whether it can demonstrate a response to medical therapy.

Study Limitations

There are several important limitations to this study. BNP levels are elevated in adults with right ventricular dysfunction and/or LV diastolic dysfunction. Because we did not perform formal evaluations of right ventricular function and LV diastolic function, we cannot exclude their influence on this cohort. Similarly, BNP concentrations may also be elevated in patients with renal insufficiency. We did not measure kidney function in this study, but no patients with a history of renal failure were enrolled. Finally, our conclusions should be tempered by the understanding that the patient sample size was small, and the numbers of adverse cardiovascular events were few. This led to widened CIs for the positive predictive value of BNP and may limit our ability to predict the occurrence of an adverse event occurring on the basis of a BNP level >300 pg/mL. More definitive conclusions about the clinical utility of BNP as a marker of circulatory com-
pensation in children with heart failure will require large, multi-institutional studies.

Summary
Whole blood BNP concentrations are increased and range widely in children with chronic LV systolic dysfunction. A subset of these patients have BNP levels that are within the normal range. More importantly, BNP concentrations can predict the 90-day composite end point of death, hospitalization, or listing for cardiac transplantation in pediatric patients with chronic LV systolic dysfunction. We speculate that BNP levels may be a useful clinical adjunct when monitoring pediatric outpatients with ventricular dysfunction, but large multicenter studies should be performed to determine the utility of BNP as a marker of prognosis and outcome.

Sources of Funding
The Biosite Triage assay and reagents were provided by Biosite Diagnostics, Inc at no cost.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

In this study we sought to determine the range of whole blood B-type natriuretic peptide (BNP) concentrations in children with chronic left ventricular systolic dysfunction and to test the hypothesis that BNP concentrations can predict adverse cardiovascular events. We found that BNP concentrations vary widely in this population and that frequently patients have levels that fall within a range considered “normal.” Despite the fact that some of these patients with chronic heart failure and normal BNP concentrations were symptomatic, none of them suffered an adverse cardiovascular event. BNP concentrations were just as reliable as, if not superior to, common echocardiographic measures of function for predicting death, hospitalization, or listing for transplantation at 90 days. Both the positive and negative predictive powers of BNP were high when a cutoff point of 300 pg/mL was used (88% and 97%, respectively). For the clinician, these findings imply that a simple blood test may serve as a reliable and relatively inexpensive adjunct tool when monitoring children with chronic heart failure in the outpatient setting. BNP concentrations appear to consistently correlate with clinical compensation in this cohort and suggest that patients with concentrations >300 pg/mL may benefit from closer surveillance. This tool may be especially useful for those patients who are too young or hesitant to verbalize their symptoms. Further investigations are needed to understand the clinical utility of serial BNP measurements in children with chronic heart failure.
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